DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

JANET WOODCOCK, M.D.

DEPUTY COMMISSIONER FOR OPERATIONS

FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

"RU-486: DEMONSTRATING A LOW STANDARD FOR WOMEN'S HEALTH?"

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES
COMMITTEE ON GOVERNMENT REFORM
HOUSE OF REPRESENTATIVES

MAY 17, 2006

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Deputy Commissioner for Operations at the Food and Drug Administration (FDA or the Agency). From 1994 to 2005, I was Director of FDA's Center for Drug Evaluation and Research (CDER). During my tenure as CDER Director, the Agency approved the drug, mifepristone, U.S. brand name, Mifeprex.

Thank you for the opportunity to discuss the Agency's role in the approval process and post-marketing activities pertaining to mifepristone. My testimony also will address FDA's adverse event reporting system and the Agency's actions in responding to adverse events reported from use of mifepristone.

REVIEW AND APPROVAL OF MIFEPREX

FDA's review and approval of the Mifeprex application adhered strictly to our legal mandate and mission as a science-based public health regulatory agency. The Agency's review complied with the Federal Food, Drug, and Cosmetic (FD&C) Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the approved labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. . ."

FDA's approval of the Mifeprex application was based on three "adequate and well-controlled" studies as that term is defined in Title 21, *Code of Federal Regulations* (CFR) section 314.126, applicable to new drug applications (NDAs) under 505(b)(1) of the FD&C Act. The Mifeprex NDA contained data from three clinical trials (a large U.S. trial and two French trials) and safety data from a post-marketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received the combination regimen of mifepristone together with the drug misoprostol). These data constituted evidence that mifepristone was safe and effective for its approved indication, the medical termination of intrauterine pregnancy through 49 days' pregnancy, in accordance with section 505(d) of the FD&C Act.

FDA's finding of drug effectiveness was based on a comparison to a historical control of the expected rate of continued pregnancy. In a historically controlled trial, listed in regulation as an acceptable type of control (see 21 CFR 314.126(b)(2)(v)), the results of treatment with the test drug are compared with experience derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies such as metastatic breast cancer and progesterone positive and unresectable meningiomas), and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

FDA's Reproductive Health Drugs Advisory Committee voted 6 to 0 (with two abstentions) on July 19, 1996, that the benefits of mifepristone exceeded the risks of the product. The Mifeprex NDA

was subjected to all levels of review within CDER and was found to be safe and effective for its approved indication.

FDA's Subpart H Regulations

The Mifeprex application was approved on September 28, 2000, under FDA's Subpart H regulations (21 CFR part 314 Subpart H). FDA approved the Mifeprex NDA under Subpart H at the sponsor's request because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use.

Under section 314.520, if FDA concludes that a drug product shown to be effective can be used safely only if distribution or use is restricted, the Agency will require post-marketing restrictions. As part of the Subpart H approval for Mifeprex, distribution of the drug was restricted in several ways, including that it must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information about Mifeprex.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an

opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.

- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex package serial number in each patient's record.

There also were a number of restrictions relating to the physical distribution system for the product. These restrictions were designed to ensure the safe use of the drug. Some complications of medical abortion are similar to those of surgical abortion, and some of these require a surgical intervention. Comprehensive risk management of abortion therefore requires that the managing physician be able to diagnose an ectopic pregnancy, manage the risks of abortion, including bleeding and infection, and be able to conduct a surgical abortion if necessary or quickly refer a patient to a provider who is trained, qualified, and readily available to do so.

In addition to distribution restrictions, the sponsor agreed to conduct two post-marketing studies, also referred to as "Phase IV commitments." These two Phase IV studies consisted of a pregnancy outcome follow-up study of women who continued to be pregnant for at least one month after any Mifeprex exposure and a prescriber monitoring study. The prescriber monitoring study was designed primarily to assess the relationship between certain post-treatment adverse events and whether the prescriber (a) provided surgical intervention if the medical abortion was not successful or

(b) referred patients to another healthcare provider for surgical abortion if the medical abortion was not successful.

Danco Laboratories, the sponsor of the Mifeprex NDA, is currently conducting the pregnancy follow-up study; it has designed and implemented a protocol, but it has determined that as of this time very few pregnancies (less than 20) were continued. For the number that were continued, Danco informs the Agency it has been unable to collect outcome data on any of them because of difficulties enrolling patients. Danco has attempted to conduct the prescriber monitoring study and has designed and implemented a protocol to that effect; however, FDA understands Danco's efforts have revealed that (1) only about 10 percent of Mifeprex prescribers were willing to participate in the study and (2) of these, more than 90 percent stated they were able to perform surgical abortions (without referral to another healthcare provider) if needed to complete a medical abortion. Thus, Danco has been unable to recruit sufficient participants to adequately power the study; furthermore, it appears that a significant majority of prescribers themselves provide any necessary surgical interventions to their patients.

The Prescriber's Agreement

The approved labeling for Mifeprex includes a Prescriber's Agreement that each potential provider is required to sign before the sponsor will distribute the product. The Prescriber's Agreement addresses the areas of expertise of the provider, the required reporting of adverse events, and the need to obtain informed consent from the patient.

Medical Expertise of the Provider - The Prescriber's Agreement requires the provider to sign a form indicating that he or she meets the qualifications outlined in the form and that he or she will observe the guidelines stated in the form. This includes agreement with the following statement:
"Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex."

These restrictions are intended to ensure that Mifeprex is prescribed by persons who are qualified to manage early pregnancy and ensure patient access to surgical abortion if that becomes necessary. Additionally, the Prescriber's Agreement states that the patient's follow-up visit at approximately 14 days is important to confirm a complete termination of pregnancy and the absence of complications.

Reporting of Adverse Events - Providers who sign the Prescriber's Agreement agree to report to the sponsor all hospitalizations, transfusions, other serious adverse events and on-going pregnancies. Prescribers either report directly to Danco's Medical Director or use a Danco 1-800 number.

Patient Informed Consent - The Prescriber's Agreement further requires that the prescriber must, consistent with the guidelines, (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, (3) give the patient the opportunity to read and discuss the Guide and Agreement, and (4) obtain the patient's signature on the Patient Agreement. The Medication Guide, which is part of the approved labeling for Mifeprex, is patient labeling designed to provide information necessary to patients' safe and effective use of the drug (see 21 CFR part 208).

Combination Regimen Including Use of Misoprostol Together with Mifepristone

FDA approved the Mifeprex NDA for the termination of early intrauterine pregnancy, defined as 49 days or less counting from the last menstrual period. The FDA-approved regimen for medical abortion consists of taking 600 milligrams (mg) (three 200 mg tablets) of mifepristone orally on Day 1 in the provider's office and 400 micrograms (mcg) (two 200 mcg tablets) of misoprostol orally on Day 3, also in the provider's office. A post-treatment examination is to be completed on approximately Day 14. FDA is aware that many medical practitioners use modified regimens, which may include prescribing different doses of mifepristone and misoprostol, dosing misoprostol on a different day, and/or advising patients that the misoprostol tablets be inserted into the vagina. While some of the modified regimens have been described in the medical literature, the safety and effectiveness of mifepristone and misoprostol dosing regimens other than the one in currently approved labeling have not been evaluated by FDA.

FDA is aware that questions have been raised about the use of misoprostol, a drug indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric

ulcers, in the medical abortion regimen with mifepristone, without a separate approval and labeling of misoprostol for this use. There are numerous other examples where the labeling of one drug recommends its use with a second drug without the approval of the sponsor of the second drug. The Agency routinely approves new drugs to be used with products already approved without requiring a change to the labeling of the previously approved drug. For example, several beta blockers and Angiotensin-converting Enzyme (ACE) inhibitors are approved for use in heart failure and in all cases, use with diuretics is recommended even though the diuretics themselves have not been separately approved for use in heart failure and do not claim this use in their labeling. The labeling for Carvedilol indicates the drug for use in treating certain types of heart failure, usually in addition to diuretics, an ACE inhibitor, and digitalis, to increase survival and decrease hospitalization.

Use of Ultrasound and Ectopic Pregnancies

In the U.S. clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, pregnancies also can be dated using other clinical methods. As mentioned previously, part of the restricted distribution of Mifeprex includes that each provider physician must state that he or she has the ability to assess accurately the duration of pregnancy and to diagnose ectopic pregnancy. The Agency determined that it was neither appropriate nor necessary for it to mandate how physicians clinically assess their patients for duration of pregnancy and for ectopic pregnancy. The approved labeling for Mifeprex recommends ultrasound evaluation as needed, leaving this decision to the physician.

Information on ectopic pregnancy was added to the WARNINGS section of the approved label in November 2004 to further alert physicians to the possibility that a patient who is undergoing a

medical abortion could have an undiagnosed ectopic pregnancy, particularly given that some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The revised label stated that:

> "No causal relationship between these events and Mifeprex and misoprostol has been established. Mifeprex is already contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."

Age of Patients Using Mifepristone

The clinical trials in the NDA excluded patients younger than 18 years old, and the labeling states that the safety and efficacy in this age group have not been studied. FDA did not require studies in pediatric patients. In the case of Mifeprex, there was no scientific reason to expect menstruating females under 18 years of age to have a different physiological outcome with the approved Mifeprex regimen from women 18 years of age and older. Since the approval of Mifeprex, literature has been published supporting the safety and effectiveness of mifepristone in females under age 18 (see Phelps R.H. et al., "Mifepristone abortion in minors" *Contraception* 64:339-43(2001)).

FDA'S ADVERSE EVENT REPORTING SYSTEM

FDA approves a new drug application if a sponsor demonstrates, through required clinical trials, that a product is safe and effective for its intended uses. The limited populations of clinical trials, however, usually do not generate all of the information about risks of a new product. Adverse effects not detected during clinical trials frequently are identified after approval through reporting to

manufacturers or directly to FDA, observational studies based on more widespread use of the product after approval, or through post-marketing clinical-trials. To account for this need, FDA created the Adverse Event Reporting System (AERS), a post-marketing drug safety program designed to collect and assess adverse events identified after approval for all drugs regulated by the Agency.

AERS consists of data from the Spontaneous Reporting System, a forerunner of the current AERS database (for reports from 1968 to October 1997) and data from AERS (for reports from November 1997 to present). AERS is a surveillance system that relies on voluntary reporting of adverse events to FDA by health care professionals and consumers, as well as reporting (some voluntary, some required by regulation) by pharmaceutical manufacturers. It includes reports from the United States and other countries of serious adverse events, non-serious adverse events, labeled adverse events (adverse events that are listed in a drug's approved labeling), and unlabeled adverse events, as well as unlabeled adverse events attributed to a drug in post-marketing clinical trials. It generally does not contain reports from clinical trials conducted prior to the approval of a product. As of April 2006, AERS contained approximately 3.5 million reports for all drugs.

When evaluating reports from the AERS system, it is important to recognize several caveats. First, accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting. Reporting to the AERS database is influenced by other factors such as duration of marketing, market share, publicity about an adverse reaction, and regulatory actions. Additionally, the AERS database often contains multiple reports of the same incident.

When FDA receives a report of a serious adverse event, the Agency carefully analyzes the available scientific information to determine whether or not the serious adverse event or death is related to the use of any of the drugs listed as possible medications. FDA staff physicians and epidemiologists evaluate the reports, investigate the seriousness of the health hazard and, if necessary, issue warnings and initiate corrective actions.

AERS Reports for Mifepristone

A total of 1,024 mifepristone *reports* have been received since the drug's approval on September 28, 2000, through March 31, 2006. However, it is important to distinguish between the total number of *reports* and the total number of *cases*, where one case refers to the collection of all reports pertaining to a single incident in a single patient. Duplicate reports often occur because the same event in the same patient is reported from more than one source (e.g., a physician sends the report directly to FDA as well as to the company, which in turn sends the report to FDA). Of these 1,024 post-marketing adverse event reports, after FDA accounted for duplicate reports, reports for use of mifepristone for indications other than termination of pregnancy (for example, treatment of certain cancers, or use in men or infants), and reports from outside the U.S., there were 950 *cases* involving mifepristone use in the U.S. in women for termination of pregnancy.

With regard to adverse event reports listing mifepristone as a possible medication, FDA has reviewed the database, identified duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details. Thus, the numbers below may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. Also, please note that these events cannot with certainty be causally attributed to mifepristone because of

information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments.

Nine hundred fifty (950) cases in women who had taken mifepristone for medical termination of pregnancy were received by FDA through March 31, 2006. According to Danco, approximately 575,000 women have been exposed to mifepristone since its approval. Most of the 950 cases listing mifepristone as a possible medication initially were submitted to FDA by the sponsor, with only 11 reports initially received by FDA directly from patients, health care providers, investigators, attorneys or family members. Approximately one-quarter of the 950 patients were hospitalized. The most frequently reported event of interest in the case reports was blood loss requiring a transfusion. The next most frequently reported events were infection and ectopic pregnancy. Approximately 40 percent of the reported 950 cases were received from three states, with 163 cases initially reported from California, 117 from New York, and 103 from Arizona, for a total of 383 cases. Approximately 94 percent of cases occurred in women aged 18 years or older, with an average age of 27 years, median age of 26 years, and a reported age range of 13-46 years. Age was unspecified in 3.8 percent of reported cases.

Cases of Heavy Bleeding

FDA has identified 116 *cases* documenting that the patient received a blood transfusion due to heavy bleeding after medical abortion. The Mifeprex U.S. labeling includes a specific warning about this adverse event in a BOXED WARNING and in the WARNINGS section.

Deaths Reported After Use of Mifepristone

FDA is aware of 12 deaths possibly involving the use of mifepristone in women. Nine of these deaths were in the U.S. Of these, five were determined to be related to infections, one involved an undiagnosed ectopic pregnancy, one appears unlikely to be related to the use of mifepristone, one was determined to be unrelated to either the medical abortion or the use of mifepristone and misoprostol, and one that is currently under investigation appears not to have involved the administration of misoprostol and appears to be unrelated to the use of mifepristone. In addition, there were three deaths in other countries related to mifepristone and misoprostol induced abortion. These 12 deaths are described below:

- Five deaths in U.S. women associated with mifepristone and misoprostol induced medical abortion, with what appears to be a rapidly fatal toxin-mediated shock syndrome
  - Four of these five, all in California, were confirmed to involve a rare anaerobic bacterium, *Clostridium sordellii (C. sordellii).* All involved the use of mifepristone 200 mg orally, followed by 800 mcg of misoprostol inserted intravaginally, a regimen that is not part of the FDA-approved labeling.
  - One U.S. woman from the west, whose death was confirmed to involve a different bacterium, *Clostridium perfringens* (*C. perfringens*). This case involved the use of mifepristone 200 mg orally, followed by 800 mcg of misoprostol inserted intravaginally, a regimen that is not part of the approved labeling.
- One death in a U.S. woman who had an undiagnosed ectopic pregnancy. Ectopic pregnancy is a contraindication for the use of mifepristone.
- One death involving a woman who initially had an unsuccessful attempted surgical abortion, followed by an unsuccessful medical abortion involving mifepristone, and then followed by a

second and successful surgical abortion. The woman was hospitalized approximately one month after taking mifepristone, and she died approximately 24 hours after admission during a hysterectomy. There was no autopsy, but pathology findings included a degenerated, pus-filled uterine fibroid. Cultures were negative for any Clostridial bacteria. Based on the available evidence at this time, FDA and the Centers for Disease Control and Prevention (CDC) do not believe this death was related to the use of mifepristone.

- One death in the northeastern U.S. was determined to be unrelated to either the medical abortion or the use of mifepristone and misoprostol.
- One death in the southwestern U.S. is still under investigation, but appears not to have involved the administration of misoprostol, and appears to be unrelated to the medical abortion or the use of mifepristone.
- One death in Canada of a woman who died during participation in a clinical trial. This death was due to sepsis involving *C. sordellii*.
- One death in Sweden of woman as a result of severe hemorrhage related to a medical abortion.
- One death of a British woman was attributed to gastric (stomach) bleeding from an ulcer.

The four California deaths, plus the Canadian case, were reported in the New England Journal of Medicine in December 2005, by CDC scientists. Since that time, CDC has been actively seeking additional cases across the country. FDA is aware that CDC has identified two additional cases which appear to be unrelated to the use of mifepristone:

- A death from the midwest in a woman who had a second trimester medical abortion employing misoprostol and laminaria (a moisture absorbing medical device inserted into the vagina to stimulate cervical dilation), but not mifepristone. This woman had *C. perfringens*.

- A toxin-mediated infectious death due to *C. sordellii* in a woman who initially was reported to have had a medical abortion. However, the woman had appendicitis and pneumonia, not a uterine infection, and CDC has been unable (despite extensive investigation) to find evidence that she had an abortion or had ever been pregnant.

The cases of women with *C. sordellii* infection are of great concern to FDA and CDC. *C. sordellii* is a rare infection and has been reported in the literature since the 1930s. The largest case series, published in 1989 by McGregor, Soper, and colleagues in the obstetrical literature, describes cases after vaginal delivery and Cesarean section, as well as a case of spontaneous endometritis. All developed a fatal shock syndrome. Other literature describes infectious illnesses in intravenous drug users and in organ transplant recipients.

FDA'S RESPONSE TO SAFETY CONCERNS RELATED TO MIFEPRISTONE

FDA has been following and evaluating safety concerns about mifepristone since its approval. As a result of ongoing monitoring of safety issues associated with mifepristone, FDA approved two revisions to the Mifeprex drug labeling and Medication Guide, in November 2004 and in July 2005. In November 2004, the black box warning was revised and strengthened to add new information on the risk of serious bacterial infections, sepsis, bleeding, and death that may occur following any termination of pregnancy, including use of Mifeprex. In July 2005, FDA approved a labeling supplement to again strengthen the black box warning on the product by noting that "atypical presentations of serious infection…can occur without fever, bacteria or significant findings on pelvic exam…." and to advise patients to seek immediate medical attention if they experience prolonged heavy bleeding.

The nature of the infection-related deaths led FDA to test for evidence of contamination in the manufacturing lots of Mifeprex and misoprostol used by the four women who died in California. The restricted distribution program for Mifeprex allowed FDA to identify the specific manufacturing lots that were involved in each case. No evidence of contamination was found and all cultures were negative.

FDA has issued public health advisories in connection with safety concerns related to mifepristone in 2004, 2005, and most recently in March 2006. FDA has consistently highlighted the fact that the cases of severe infection occurred with regimens of mifepristone and misoprostol that were not in approved labeling, although the relationship of the infections to such use remains unknown.

FDA has sought expert advice and consultations to evaluate scientific issues from both inside and outside the Agency. To supplement the ongoing evaluation and expertise of CDER's Office of Drug Safety and Division of Reproductive and Urologic Products, FDA consulted with its Division of Anti-Infective Drug Products. FDA also consulted with outside obstetricians/gynecologists and maternal-fetal medicine experts and CDC, ultimately leading to the detailed microbiology testing and documentation of *C. sordellii* as the underlying organism involved in the four cases from California. These cases have led to CDC investigations across the country in search of additional cases, including their initiation of a detailed search concerning all maternal deaths in the state of California. These investigations are ongoing, but the national search for *C. sordellii* cases in association with maternal death has already identified, in addition to those described above with medical abortion, three cases in women who recently had a miscarriage (spontaneous abortion). These occurred in the midwestern, western, and northeastern U.S.

It is noteworthy that over the time period that *C. sordellii* was being identified as a source of rare, infection-related deaths following medical abortion, CDC was investigating unusual outbreaks of another Clostridium species, *Clostridium difficile (C. difficile)*. Unlike *C. sordellii*, *C. difficile* is a common infection in the U.S., with an estimated incidence of up to 500,000 cases per year, mostly in hospitals and following use of antibiotics. The infection, which also is mediated by a toxin produced by the bacterium, typically causes severe diarrhea and fever. In recent years, however, cases associated with a severe, sepsis-like illness have increasingly been reported, and most recently such cases have been reported in healthy individuals, four in pregnant women, with no recent hospitalization or history of antibiotic use, suggesting a newly emerging serious toxin-mediated illness (with many similarities to the fatal cases of *C. sordellii*).

To help address the questions and issues that would allow for a better understanding of *C. sordellii* infection, it was clear to FDA that expertise in other Clostridial diseases and microbiology, as well as experts on the effects of drug exposure in both conditions, was essential. This led FDA to initiate a scientific workshop in collaboration with CDC and the National Institute for Allergy and Infectious Diseases to bring together such scientific and public health experts. It was clear to FDA and its sister agencies that all involved needed to collaborate to better understand the risk factors contributing to reports of morbidity and mortality associated with *C. sordellii* and *C. difficile*, and that further research was likely to be needed. This workshop, "Emerging Clostridial Diseases," was held Thursday, May 11, 2006, in Atlanta, Georgia.

Emerging Clostridial Diseases Workshop

The goal of this public workshop was to identify research needs and priorities in order to enable progress in understanding the virulence, pathogenesis, host factors, and nonantimicrobial risk factors contributing to reports of morbidity and mortality associated with *C. sordellii* and *C. difficile*. Three panels, consisting of medical and/or public health representatives from federal government (FDA, CDC, and the National Institutes of Health), state governments, and academia, presented data and discussed a number of the complex issues surrounding these two related anaerobic bacteria.

1. **Clinical Syndromes, Pathophysiology and Host Factors** – Nine presenters discussed various clinical aspects of both *C. sordellii* and *C. difficile*.
2. **Surveillance for Disease and Sources of Infection** – Two presenters discussed related disease surveillance initiatives at both the federal and state levels
3. **Identifying a Research Agenda** – The final discussion consisted of a general discussion among workshop presenters, as well as the audience, regarding recommendations for research agenda priorities for:

- Surveillance and epidemiology;
- Basic research; and
- Diagnosis, treatment, and prevention.

There appeared to be broad consensus that additional research is necessary to improve our clinical understanding of both *C. sordellii* and *C. difficile.* Participants also stressed that surveillance and communication efforts should continue to be refined and focused on enhancing the epidemiological data about, and awareness among clinicians of, both diseases. The workshop served as an important first step in advancing our understanding of some of the most critical underlying questions

surrounding mifepristone, *C. sordellii*-related deaths, and a potential association between the two. It also underscored the fact that there are additional important questions to be asked and clinically investigated regarding, for example, toxin production and potential antibiotic use in association with mifepristone. While an exact pathway forward, and a precise timeline, are unclear at this point, FDA is committed to continuing to work with others, both within and outside of the federal government, to improve our knowledge of these dangerous diseases and the public health concerns they raise.

CONCLUSION

FDA's mission is to protect and promote the public health by ensuring that marketed drugs are safe and effective for their approved indications. The American people have come to expect this gold standard, and the Agency remains dedicated to fulfilling this important responsibility. FDA is a science-based public health regulatory agency, and the foundation of the drug approval process is sound scientific rigor. FDA takes all reports of adverse events seriously, and the Agency finds none more troubling than reported grave injuries to, or deaths of, otherwise healthy patients. Mifeprex post-marketing adverse event data are being evaluated on an ongoing basis. These data will continue to inform the risk-benefit profile of this drug, including consideration of the risks associated with other alternatives. FDA will continue to communicate to the public, healthcare practitioners, and patients emerging safety information that becomes available that would assist them in making proper choices regarding their health.